

## Refine Search

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| L3 and (424/450).ccls. | 35        |

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L4

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| <u>L4</u> | L3 and 424/450.ccls.                                  | 35  | <u>L4</u> |
| <u>L3</u> | (liposome) and (ammonium adj1 sulfate) same (sucrose) | 231 | <u>L3</u> |
| <u>L2</u> | (lipid adj1 film) and (ammonium same sucrose)         | 54  | <u>L2</u> |
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L2: Entry 22 of 54

File: PGPB

Aug 12, 2004

DOCUMENT-IDENTIFIER: US 20040156888 A1

TITLE: Liposomal formulations

Detail Description Paragraph:

[0103] Lipid films or lipid spray dried powder containing various phospholipids including hydrogenated soy phosphatidyl choline (HSPC), dioleoyl phosphatidyl choline (DOPC), dielaidoyl phosphatidyl choline (DEPC), cholesterol (Chol) and distearoylphosphatidylglycerol (DSPG) at the following mole ratios were prepared.

Detail Description Paragraph:

[0108] Lipid Film Preparation.

Detail Description Paragraph:

[0109] Stock solution of each lipid component was made in a chloroform: methanol 1:1 (v/v) organic solvent system. The final concentration of each lipid component was: HSPC, DOPC, DEPC and Chol (200 mg/ml); and DSPG (50 mg/ml). Lipid solutions were pipetted according to the designed mole ratio and were mixed in a conical tube. The final lipid concentration was around 200 mg/ml. The solvent was then removed by running nitrogen through the solution while the solution was heated in heat block with temperature set at 65 C. The formed lipid film was then left in desiccator under vacuum to remove residual organic solvent till being used.

Detail Description Paragraph:

[0114] Preparation of Liposomes by Probe Sonication from Either Lipid Film or Spray Dried Lipid Powder

Detail Description Paragraph:

[0115] Lipid film or lipid powder was weighed out and hydrated with CDDP stock solution in a 70.degree. C. water bath at lipid concentration approximately 150 mg/ml. The hydrated solution was subjected to probe sonication until the solution became translucent. A typical temperature of sonication was 70.degree. C. and a typical sonication time was 15 to 20 minutes. After completion of sonication, the liposomes were subjected to one of the following cleaning procedures: a) the liposomes were cooled down to ambient temperature for around 4 hours, and the yellow precipitation was removed by centrifugation, and the precipitation-free clear solution was applied to a sephadex G-50 column for buffer exchange with 9% sucrose; or b) upon completion of sonication, the liposomal solution was immediately diluted one to ten with 200 mM sodium chloride solution; that diluted solution was subjected to ultra filtration for cleaning/buffer exchange with 9% sucrose; and the sterilization filtration of the liposome solution was made at ambient temperature through a cellulose acetate 0.22 micron filter.

Detail Description Paragraph:

[0121] Preparation of Liposome by Probe Sonication from Either Lipid Film or Spray Dried Lipid Powder

Detail Description Paragraph:

[0125] Preparation of Liposome by Probe Sonication from Either Lipid Film or Spray Dried Lipid Powder

Detail Description Paragraph:

[0126] A proper amount of lipid was weighted out. The lipid was hydrated with Vancomycin stock solution at 300 mg/ml lipid concentration. The mixture was sonicated at around 60.degree. C. for 20 minutes or until the solution became transparent. Upon completion of sonication, the liposome solution was diluted 1:1 with acidic 9% Sucrose. The post diluted liposome solution was then passed through sephadex column to remove free drug by buffer exchanging with 10 mM Ammonium Chloride in 9% Sucrose pH=6.5. The liposomes were filtered at ambient temperature through a cellulose acetate 0.22 micron filter. Characterization data for representative liposomes is shown in the following table.

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L2: Entry 27 of 54

File: PGPB

Jul 17, 2003

DOCUMENT-IDENTIFIER: US 20030133972 A1

TITLE: Targeted multivalent macromolecules

Detail Description Paragraph:

[0219] FIG. 17 outlines the formation of the nanoparticles (PVs) by self-assembly and polymerization of the appropriate lipids as previously described in Storrs, et al., *ibid*. The trivalent lipid-integrin antagnoist 12 was combined with commercially available diacetylene phospholipid 13 and the europium-chelator lipid complex 14 in a chloroform solution. Compound 14 was added at one percent to all formulations in order to visualize the particles using Fluorescence spectroscopy. Orellana, et al., *Biochim. Biophys. Acta* (1996) 1284:29-34. To this solution was added either the anionic chelator lipid 15 or the cationic lipid 16 in order to vary the surface charge and provide a surface to chelate radionuclides. Storrs, et al., 1995b. The surface density of the integrin antagonist on the PVs was controlled by varying the concentration of compound 12. To form vesicles, the combined lipid solutions were evaporated to dryness and dried under high vacuum to remove any residual solvent. The dried lipid film was hydrated to a known lipid density (30 mM) using deionized water. The resulting suspension was then sonicated at temperatures above the gel-liquid crystal phase transition ( $T_{sub.m.} \approx 64^{\circ}C$ ) using a probe-tip sonicator while maintaining the pH between 7.0 and 7.5. Spevak, W. R. Doctoral Thesis, University of California at Berkeley, 1993; Leaver, et al., *Biochim. Biophys. Acta* (1983) 732:210-218. After approximately one hour of sonication the solution became clear. The vesicles were then polymerized by cooling the solution to  $0^{\circ}C$  on a bed of wet ice and irradiating the solution at 254 nm with a hand-held UV lamp for two hours. The resulting PVs (PV1 through PV6) were yellow-orange in color and had two visible absorption bands centered at 490 nm and 535 nm arising from the conjugated ene-yne diacetylene polymer. Storrs, et al., 1995a. The mean diameter of the PVs were between 40 nm and 50 nm as determined by dynamic light scattering (DLS) and the zeta potential was between -42 and -53 mV for PV1 through PV4 and +35 and +43 mV for PV5 and PV6 respectively (Brookhaven Instruments, Holtsville, N.Y.). The PVs were stable for months without significant changes in the physical and biological properties when formulated for in vivo applications using 150 mM sodium chloride, 50 mM histidine, and 5% dextrose solutions. Properties of exemplary PVs are shown in Table Z.

Detail Description Paragraph:

[0228] Quantitative encapsulation of doxorubicin at 0.15 and 1.5 mg/mL was achieved in 10% sucrose solution using vesicles (15 mg/mL) containing 250 mM ammonium sulfate as described in EXAMPLE 11-EXAMPLE 14. Targeted delivery of doxorubicin by ITLs was demonstrated with murine endothelial cells (MECs) in an in vitro cell proliferation assay described in, but the murine tumor cells were resistant to treatment under identical assay conditions. For MECs, incubation with ITLdox resulted in 4-fold higher reduction in cell density than untargeted Ldox. ITLs without doxorubicin had no effect on cell proliferation. Doxorubicin at identical concentrations also resulted in significant reductions in cell proliferation, but analysis of the vesicles by size exclusion chromatography shows that reductions in cell proliferation were not due to release of doxorubicin from ITLdox.

Detail Description Paragraph:

[0249] BisT-PC 13 (500 mg, 546.9  $\mu$ mole, 95 mole %) was weighed into a clean 100 ml round bottom flask. Chelator lipid 15 (3.15 ml, 31.5 mg, 23  $\mu$ mole, 4 mole %), and RGD peptidomimetic lipid 12 (1.54 ml, 15.4 mg, 5.74  $\mu$ mole, 1 mole %) were added to the flask by glass syringe. Chloroform was removed by rotary evaporation. The lipid film was hydrated with 20 ml of 250 mM ammonium sulfate and 190  $\mu$ l 0.5 N NaOH while rotating the flask in the 65.degree. C. water bath. Immediately prior to extrusion, the lipid suspension was briefly sonicated in the 100 ml flask to reduce the size of the aggregates and then transferred to the extruder. The lipid suspension was extruded through a series of successively smaller pore size polycarbonate (PC) membranes. The 10 ml thermal barrel extruder maintained at 90.degree. C. was fitted with 2 stacked membranes and the lipid suspension was extruded through 100 nm membranes, then 50 nm membranes, and finally 30 nm membranes using argon at 300-600 p.s.i. The vesicles were transferred to dialysis cassettes and dialyzed against 10% sucrose (2.times.1800 ml, 4 h). The size determined by dynamic light scattering was approximately 60 nm.

Detail Description Paragraph:

[0252] Integrin-targeted liposomes containing ammonium sulfate from EXAMPLE 8 (2 mL, 60 mg) were placed in a 12.times.100 mm glass culture tube and 600  $\mu$ l (6 mg) doxorubicin in 10% sucrose was added. The mixture was incubated for 5 minutes at 65.degree. C. and size exclusion chromatography (SEC) showed that the loading of doxorubicin was quantitative. SEC analysis was performed with 10 mM HEPES buffer containing 200 mM NaCl pH 7.4 by adding a 100  $\mu$ l sample from the doxorubicin loading mixture to a Sepharose CL 4B column (1.5.times.6 cm). The mixture was diluted with 10% sucrose to give a final vesicle concentration of 15 mg/ml. These vesicles contain 10% doxorubicin by weight. The size measured by dynamic light scattering was 60-65 nm.

Detail Description Paragraph:

[0253] Integrin-targeted liposomes containing ammonium sulfate from EXAMPLE 8 (2 mL, 60 mg) were placed in a 12.times.100 mm glass culture tube and 60  $\mu$ l (0.6 mg) doxorubicin solution added. The tube was immersed in a water bath maintained at 65.degree. C. for 5 minutes. The mixture was diluted with 10% sucrose to give a final vesicle concentration of 15 mg/ml. SEC analysis was performed as described in EXAMPLE 11 and showed that all doxorubicin added was encapsulated in the liposome. These vesicles contain 1% doxorubicin by weight. The size measured by dynamic light scattering was 60-65 nm.

Detail Description Paragraph:

[0256] BisT-PC (1 g, 1093.7  $\mu$ mole, 95 mole %) and N-succinyl-DPPE (47 mg, 57.6  $\mu$ mole, 5 mole %), were weighed into a clean 100 ml round bottom flask and dissolved in 20 ml chloroform. Chloroform was removed by rotary evaporation. The lipid film was hydrated with 40 ml 250 mM ammonium sulfate and 500  $\mu$ l 0.5 N NaOH while rotating the flask in the 65.degree. C. water bath. The pH after hydration was 7.5. Vesicles were prepared with a thermal barrel extruder at 65.degree. C. by passing the solution through two stacked membranes with pore sizes of 100 nm (400 psi argon), then 50 nm membranes (400 psi argon), and finally 30 nm membranes (700 psi argon). The vesicles were transferred to dialysis cassettes and dialyzed against 10% sucrose. The size determined by dynamic light scattering was approximately 68 nm. This procedure was also used without the addition of sodium hydroxide to prepare vesicles containing 10 mole percent of the N-succinyl-DPPE lipid, 50 mole percent of dimyristoyl-sn-glycero-3-phosphocholine (DMPC), dipalmitoyl-sn-glycero-3--phosphocholine (DPPC), or distearoyl-sn-glycero-3-phosphocholine (DSPC), and 40 mole percent cholesterol.

Detail Description Paragraph:

[0266] A dried lipid film containing BisT-PC (1 g, 1093.7  $\mu$ mole, 95 mole %) and N-succinyl-DPPE (47 mg, 57.6  $\mu$ mole, 5 mole %) was prepared by rotary evaporation of a chloroform solution. The dried film was hydrated by addition of 250 mM ammonium sulfate and warming in a 65.degree. C. water bath for 30 minutes. The

hydrated lipid suspension was then extruded through a series of successively smaller pore sized polycarbonate track etched filter membranes using a thermal barrel extruder maintained at 65.degree. C. Extrusion was initiated with a 100 nm pore size filter and terminated with a 30 nm pore size filter. Excess ammonium sulfate was removed by dialysis in 10% sucrose solution. The vesicles were coated with aminodextran, succinylated, and coupled to integrin antagonist 10 by the procedure described in Examples 17-19. Doxorubicin was loaded into the vesicles by mixing with a sucrose solution of doxorubicin and warming the mixture to 65.degree. C. for 5 minutes. In a typical preparation, doxorubicin at 10 mg/mL in 10% sucrose solution was added to 1 mL of vesicles containing ammonium sulfate. Complete uptake of the added doxorubicin was confirmed by SEC on a column of Sepharose CL 4B equilibrated and eluted with 10 mM HEPES, 200 mM NaCl pH 7.4.

Detail Description Paragraph:

[0267] Succinylated dextran-coated vesicles containing BisT-PC (1 g, 1093.7 .mu.mole, 95 mole %) and N-succinyl-DPPE were prepared as described in EXAMPLE 20, except no ammonium sulfate was used. The RGD mimetic 10 was coupled to these vesicles as described in EXAMPLE 19. The resulting RGD mimetic-dextran vesicle conjugates were suspended in 250 mM ammonium sulfate solution and heated to 65.degree. C. for 30 minutes. Excess ammonium sulfate was removed by dialysis with 10% sucrose solution. Doxorubicin was loaded into the vesicles by mixing with a sucrose solution of doxorubicin and warming the mixture to 65.degree. C. for 5 minutes. In a typical preparation, doxorubicin at 10 mg/ml in 10% sucrose solution was added to 1 ml of vesicles containing ammonium sulfate. Uptake of the added doxorubicin was confirmed by SEC on a column of Sepharose CL 4B equilibrated and eluted with 10 mM HEPES, 200 mM NaCl pH 7.4.

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR

L1 liposome same (hydrat\$) same ammonium same (sucrose or sugar or  
 \$saccharide)

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L1

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L1: Entry 23 of 25

File: USPT

Feb 3, 1998

DOCUMENT-IDENTIFIER: US 5714163 A

TITLE: Vinca alkaloid vesicles with enhanced efficacy and tumor targeting properties

Detailed Description Text (13):

This example details the entrapment of vincristine into neutral vesicles, e.g., distearoylphosphatidylcholine:cholesterol, 2:1 molar ratio. This example further details the efficacy of neutral liposomes. Vesicles were prepared by hydrating approximately 500 mg of sprayed-dried lipids, DSPC:CHOL (2:1, mole ratio), at 65.degree. C. with either a buffer containing the ammonium salt of one of the counterions or 300 mM sucrose. The lipid concentration was approximately 100 mg/ml. The hydrating buffers consisted of (1) 150 mM ammonium glutamate; (2) 100 mM ammonium tartrate; (3) 150 mM ammonium dihydrogen pyrophosphate; (4) 150 mM ammonium aspartate; (5) 100 mM ammonium ethylenediaminetetraacetic acid; (6) 100mM ammonium succinate; (7) 100 mM ammonium pyrophosphate; (8) 150 mM concentration ammonium lactobionate; (9) 75 mM ammonium citrate; and (10) ammonium sulfate. The hydrated lipids were sonicated at 65.degree. C. for about 20 minutes with a probe sonicator. The vesicles were annealed for 10 minutes at 65.degree. C., cooled to room temperature (RT), centrifuged 10 minutes at 3500 RPM, and subjected to a buffer exchange by gel filtration on a 60 cm G50-80 Sephadex column previously equilibrated with unbuffered 300 mM sucrose. Concentration of the lipids was determined by HPLC. The liposomes were then stored at room temperature overnight.

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L1: Entry 21 of 25

File: USPT

Apr 18, 2000

DOCUMENT-IDENTIFIER: US 6051251 A

TITLE: Liposome loading method using a boronic acid compound

Detailed Description Text (53):

The liposome suspension was prepared by dissolving the lipids in ethanol and drying the lipids to a thin film. The lipid film was hydrated with an ammonium sulfate solution to form liposomes and then the liposomes were extruded to obtain liposomes of about 100 nm. The liposome suspension was dialyzed against a sucrose solution, thus obtaining liposomes encapsulating a 250 mM ammonium sulfate solution in an external buffer of 10% sucrose at pH 6.5. The total lipid concentration was 52 .mu.moles/ml.

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L1: Entry 20 of 25

File: USPT

Aug 29, 2000

DOCUMENT-IDENTIFIER: US 6110491 A

TITLE: Compound-loaded liposomes and methods for their preparation.

Detailed Description Text (92):

Aqueous solutions containing ammonium salts of hydrochloric, nitric, methanesulfonic, L(+)-tartaric, citric, sulfuric, phosphoric, diethylenetriamine pentaacetic (DTPA), or polyacrylic (Mol. weight. 2,000) acids were prepared by titration of the respective acids in water with the standard aqueous solution of ammonium hydroxide to achieve pH 7.3+-.0.05, followed by volume adjustment to achieve 0.2 equivalent/L of ammonium ion, and, if necessary, by addition of dry sucrose to achieve osmolarity of 377 mmol/kg. (These solutions are hereinafter referred to as Inner Buffers). All solutions additionally contained 10 mM hydroxyethylpiperazinoethane sulfonic acid (HEPES) to stabilize the pH at titration endpoint. To afford determination of intraliposomal pH, a fluorescence indicator 8-hydroxypyrene trisulfonate was added to the solutions to the final concentration of 0.2 mM. Liposomes containing entrapped ammonium salt solutions as above were prepared from egg phosphatidyl choline, cholesterol, and PEG-DSPE as described in the Example 7, except that lipid hydration and extrusion were carried out at room temperature. The bulk aqueous phases of liposome preparations were exchanged by gel-filtration for an aqueous solution (Outer buffer) containing 0.2 M ammonium chloride, 10 mM HEPES, pH 7.3, osmolarity 377 mmol/kg, to obtain liposome preparations substantially without transmembrane ammonium-ion gradients. Loading of doxorubicin was performed as in Example 7, except that it was at 36.degree. C. for 12 hours. Intraliposomal pH was determined using HPTS fluorescence method (Straubinger, et al., 1990) prior to drug loading, and indicated essentially no inside-outside pH gradient (less than 0.2 pH units), compared with the gradient of several pH units typical for ammonium ion gradient liposomes (Haran, et al., 1993). The following results were obtained (nd, not determined)

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L1: Entry 10 of 25

File: PGPB

Aug 12, 2004

DOCUMENT-IDENTIFIER: US 20040156888 A1

TITLE: Liposomal formulations

Detail Description Paragraph:

[0126] A proper amount of lipid was weighted out. The lipid was hydrated with Vancomycin stock solution at 300 mg/ml lipid concentration. The mixture was sonicated at around 60.degree. C. for 20 minutes or until the solution became transparent. Upon completion of sonication, the liposome solution was diluted 1:1 with acidic 9% Sucrose. The post diluted liposome solution was then passed through sephadex column to remove free drug by buffer exchanging with 10 mM Ammonium Chloride in 9% Sucrose pH=6.5. The liposomes were filtered at ambient temperature through a cellulose acetate 0.22 micron filter. Characterization data for representative liposomes is shown in the following table.

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L1: Entry 9 of 25

File: PGPB

Dec 23, 2004

DOCUMENT-IDENTIFIER: US 20040258747 A1

TITLE: Tumor-targeted drug delivery systems and uses thereof

Detail Description Paragraph:

[0132] In the simplest approach for generating an ion gradient, the hydrated, sized liposomes have a selected internal-medium pH. The suspension of the liposomes is titrated until a desired final pH is reached, or treated as above to exchange the external phase buffer with one having the desired external pH. For example, the original medium may have a pH of 5.5, in a selected buffer, e.g., citrate buffer or ammonium sulfate buffer, and the final external medium may have a pH of 8.5 in the same or different buffer. The internal and external media are preferably selected to contain about the same osmolarity, e.g., by suitable adjustment of the concentration of buffer, salt, or low molecular weight solute, such as sucrose.

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L1: Entry 8 of 25

File: PGPB

Feb 3, 2005

DOCUMENT-IDENTIFIER: US 20050025822 A1

TITLE: Method of pulmonary administration of an agent

Detail Description Paragraph:

[0063] HSPC, cholesterol and, in some formulations, mPEG-DSPE were solubilized in ethanol. Multilamellar vesicles were formed using the ethanol injection technique where the ethanol solution of lipids were hydrated in ammonium sulfate at pH 5.5 and at 65.degree. C. Liposomes were downsized to .about.150 nm by extrusion through an extruder at 65.degree. C. using serial size decreasing membranes --0.4 .mu.m, 0.2 .mu.m and 0.1 .mu.m. External ammonium sulfate was removed by exchanging against 10% sucrose, NaCl (pH=5.5) using diafiltration to generate an ion gradient. Ciprofloxacin was solubilized in 10% sucrose and incubated with the liposomes at 65.degree. C. for 30-60 min. Free ciprofloxacin was removed using diafiltration against 10% sucrose, NaCl. Typical loading resulted in 40-60% of initial drug concentration loaded into liposomes. The final solution was in a 10 mM histidine and 10% sucrose buffer. Typical drug to lipid ratios were 0.3-0.5 (w/w).

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